Universität Basel

Research Project

Cyst wall formation: a persistent challenge in Toxoplasmosis

Third-party funded project

Project title Cyst wall formation: a persistent challenge in Toxoplasmosis
Principal Investigator(s) Bumann, Dirk ;
Project Members Li, Jiagui ;
Organisation / Research unit
Departement Biozentrum / Molecular Microbiology (Bumann)
Department
Project start 01.08.2015
Probable end 31.07.2018
Status Completed

The acute phase of Toxoplasma gondii infection initiates with the rapid proliferation and dissemination of the fast-replicating form of the parasite (tachyzoite) throughout the vertebrate host. At the onset of the immune response, the tachyzoites are efficiently neutralized and the infection enters in a chronic phase with conversion to a slow-replicating developmental stage (bradyzoite) that forms tissue cysts predominantly in the central nervous system and in striated and heart muscle. This process of encystation is vital to the parasite's life cycle because i) it ensures survival and life-long persistence in intermediate hosts, and ii) it allows peroral transmission to the feline definitive host, initiating the sexual cycle. Tissue cysts not only prevent eradication of the parasite, but also pose a significant threat of reactivation in the context of host immunosuppression and can lead to encephalitis and other severe clinical manifestations. Despite the central importance of cyst formation for pathogenesis and transmission, our insight into how T. gondii defies the innate and adaptive immune responses to take up permanent residence in the immunocompetent hosts is rudimentary. Very little is known about the cyst wall composition and the molecular processes governing its formation. We have a very fragmented view of the temporal and spatial dissemination of cysts in the host and especially in the brain. Progress in biology is driven both by medical necessity and scientific curiosity and this project, which proposes to investigate the process of encystation, lies at the intersection of these two forces. It is the most propitious time to address the challenging question of cyst wall formation in light of the most recent breakthroughs in the sensitivity of -omics approaches, the power of the CRISPR/Cas9 system in genome editing, the revolution in high-throughput microscopy, and ex-vivo tissue examination at the highest level of resolution. This ambitious and highly synergistic project tackles key biological questions on tissue cyst formation and capitalizes heavily on cutting-edge technologies to address three specific objectives: 1. A comprehensive definition of the cyst wall composition. We will generate an unprecedentedly accurate transcriptome of the bradyzoite stage and a differential proteome of bradyzoites and the surrounding cyst wall. The data will be curated via a powerful comparative genomics approach spanning cyst-forming and cyst-lacking Apicomplexa species. A complementary mutagenesis and selection strategy is designed to identify specific defects in cyst formation or maturation by large-scale genetic screens using quantitative high-throughput microscopy. 2. An uncovering of molecular mechanisms governing the cyst wall formation. This aim will be accomplished by taking a targeted as well as a global functional approach. Starting from recent findings on parasitophorous vacuole formation of tachyzoites we will implement a semi-targeted gene knockout- or conditional knockout approach. Moreover, the creation of a comprehensive gene disruption collection in subproject 1 will allow identification of all non-essential tachyzoites genes that display trafficking defects during cyst formation. Key mutants will be mechanistically dissected in vitro with a subset to be investigated further in vivo. 3. A spatiotemporal cartography of cyst formation in the brain. We will

harness cutting-edge imaging methods to investigate the in vivo dynamics of dissemination and cyst formation in the whole body and foremost in the brain of a mouse infection model. These findings will inform development of spatiotemporal models describing parasite dissemination and differentiation, to be correlated with data from post-mortem biopsies. By combining unbiased and targeted experimental approaches, we are poised to achieve major conceptual advances in deciphering the molecular events leading to cyst wall formation. In the long term, the data and technology created in this project will lay the foundation to decoding the molecular information exchange between host and pathogen during establishment of life-long latent infections. These studies fill a significant knowledge gap and will provide i) highly valuable web-accessible integrated gene expression data, ii) fundamental discoveries about the regulatory and trafficking circuits that govern formation of the cyst wall as a biological barrier during encystation iii) invaluable paradigms of how the parasite initiates and sustains molecular programs required for disease progression and persistence.

Keywords Toxoplasma gondii, Cyst-wall, Virulence, Apicomplexa, Persistence, Transmission
Financed by
Swiss National Science Foundation (SNSF)

Add publication

Add documents

Specify cooperation partners

ID	Kreditinhaber	Kooperationspartner	Institution	Laufzeit - von	Laufzeit - bis
3396125	Bumann, Dirk	Hehl, Adrian, Professor	Universität Zürich	01.10.2015	30.09.2018
3396127	Bumann, Dirk	Soldati-Favre, Dominique, Professor	Université de Genève	01.10.2015	30.09.2018